

## Format for ANSWERING REVIEWERS



Feb 11th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7592-review.doc).

**Title:** Preoperative Biliary Drainage in Hilar Cholangiocarcinoma: When and How?

**Author:** Woo Hyun Paik, Nerenthiran Loganathan, Jin-Hyeok Hwang

**Name of Journal:** *World Journal of Gastrointestinal Endoscopy*

**ESPS Manuscript NO:** 7592

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

### **Reviewer #1:**

Dear Editor: Thanks for giving me the opportunity to review the manuscript "Preoperative Biliary Drainage of hilar Cholangiocarcinoma: When and How?" submitted by Woo Hyun Paik and colleagues to the World Journal of Gastrointestinal Endoscopy. The Authors elegantly summarize the current (limited) evidence for clinical guidance in terms of preoperative endoscopy management in hilar cholangiocarcinoma. They have included the relevant original literature (including purely retrospective studies) and, thoughtfully, have attempted to suggest endoscopic management strategies in specific clinical situations in this rare tumor type with overall low resectability rates. There are minor concern/suggestions to be raised, however:

1) Overall, the language level has to be improved in some sections of the manuscript: e.g. abbreviations should be rigorously introduced prior to being used (compare usage of ENBD in the Core Tip section), in addition, there are some terms that are not in broad use in the English literature, e.g. cholestasis-associated hepatic toxicity (which might be changed to cholestasis-associated/-related liver dysfunction). Taken together, it is felt that the manuscript would benefit from being critically revised by a native speaker.

According to the reviewer’s suggestion, the manuscript was revised again by a native speaker. We embedded a language certificate by professional English language editing company. We also changed the “cholestasis-associated hepatic toxicity” to “cholestasis-associated liver dysfunction”.

2) Given the complex suggestions relative to different categories of clinical constellations, the differential indications of the distinct endoscopic procedures suggested by the Authors should be summarized in a Table. Otherwise, the manuscript is sound in respect of its content and addresses a relevant, though challenging clinical issue.

We embedded the recommended indications of preoperative biliary drainage and selective biliary drainage in hilar cholangiocarcinoma in TABLE 2.

TABLE 2. Recommended indication for preoperative biliary drainage and total biliary drainage in hilar cholangiocarcinoma

<b>Preoperative biliary drainage</b>	Right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma
	Preoperative portal vein embolization and chemoradiation therapy
	Biliary infection of undrained bile duct
	Severe pruritus
<b>Total biliary drainage</b>	Development of cholangitis after selective drainage
	Slow resolution of hyperbilirubinemia
	Opacification of bilateral intrahepatic bile duct

**Reviewer #2:**

This manuscript by Paik et al reviews the literature regarding pre-op biliary drainage for surgical candidates with malignant bile duct obstructions. The manuscript is overall well done, but requires some revisions to meet publication standards.

**Overall: Please review for language and grammar throughout. There are a number of issues.  
“effective better option”**

We previously answered to the Review #1’s question. Please make sure the prior response.

**Core Tip: the core tip uses some abbreviations (ENBD and PTBP) that have not yet been defined in the text. I’m not sure where this will come in the published manuscript, so these may or may not need to be defined here.**

According to the comment, the abbreviations were defined in Core Tip section.

**Intro: you state that bile duct resection with hepatectomy achieves a “higher radical resection rate”. This is simply the definition of a radical resection. I think you mean to say it achieves a higher cure rate.**

In order to eliminate misunderstandings, we changed the expression according to your comments.

“This treatment modality achieves a higher cure rate compared to that with bile duct resection alone”

**Intro: if a meta analysis recently demonstrated no clinical advantage and several clinical disadvantages to PBD, why are you recommending it at all in this manuscript. Are there certain circumstances that this meta analysis did not address. If so, you should really focus your intro and conclusions to address this issue**

We do not recommend PBD routinely as the systematic review (Liu et al., Dig Dis Sci 2011;56:663-672) had concluded. However, in certain clinical settings, PBD should be considered. Liu et al. suggested that PBD should be performed prior to portal vein embolization for the hypertrophy of future remnant liver. We totally agree with their opinion, and we address some other conditions when PBD is recommended. We made up the TABLE 2 which contains the special indication of PBD in hilar cholangiocarcinoma as follows:

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<b>Preoperative biliary drainage</b>	Right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma
	Preoperative portal vein embolization and chemoradiation therapy
	Biliary infection of undrained bile duct
	Severe pruritus

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We also emphasized the recommended indication of PBD in CONCLUSION section according to your comments.

Under certain special indications such as right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended.

**Intro: please list your methods. How did you identify the studies you cite. How did you ensure you did a thorough literature review, etc.**

We searched electronic databases with the following keywords: “hilar cholangiocarcinoma”, “Klatskin tumor”, and “biliary drainage”. The results of studies about preoperative biliary drainage in hilar cholangiocarcinoma from 1999 were listed in our manuscript. We mentioned about this in INTRODUCTION section as follows:

“We searched electronic databases with the following keywords: “hilar cholangiocarcinoma”, “Klatskin tumor”, and “biliary drainage”. The studies about preoperative biliary drainage in hilar cholangiocarcinoma from 1999 are reviewed and listed in this study.”

**Optimal period of drainage: how does ERBD delay surgery? Are patients just more comfortable with delay because they don't have a nasal or abdominal tube to deal with? Do you (in practice) perform ENBD over ERBD for these patients?**

We can notice the tube malfunction of ENBD or PTBD earlier by monitoring the amount of bile. However, it is impossible to recognize the malfunction of ERBD until cholangitis or pruritus has developed. It means that the treatment of ERBD malfunction could be delayed. Moreover, ERBD can cause bacterial translocation into the bile duct. For these reasons, ERBD may delay the surgery, and we prefer ENBD over ERBD in clinical practice.

**Reviewer #3:**

This is a good review regarding preoperative biliary drainage for hilar obstruction.

Major issues

**The main issue with this review is the heterogenous amount of data you are evaluating: all these studies have very different drainage-related morbidity, postoperative mortality, preoperative bilirubin levels, preoperative liver function/volumen (when assessed). I would try to analyse this problem in more details if you wish to make the reading more interesting. No one wants to use a preoperative drainage, but it is often necessary, which is probably why your conclusions don't match the meta-analysis conclusion.**

As you commented, the main limitation of analyzing the previous data is the lack of uniformity. We tried to analyze the previous data to find the factors of PBD affecting clinical outcome, however, each studies showed variety of inconsistent results. This may be due to some important variables which

affect clinical outcomes are not controlled since almost studies were performed in retrospective nature. Preoperative drainage should not be used indiscriminately. However, in certain special situations, PBD should be considered. We mentioned about the special indication when preoperative biliary drainage or total biliary drainage is necessary in TABLE 2.

Minor issues:

**Please review the manuscript for english language**

According to the reviewer's suggestion, the manuscript was revised again by a native speaker.

**Please define radical resection for hilar cholangiocarcinoma (does that include extended hepatectomies only, what about routine portal vein resection)**

Extended hepatic parenchymal resection is performed to achieve negative resection margins microscopically. In some high-volume centers with experienced surgeons, major vascular resection (particularly portal vein) is also performed to achieve histologically negative margins of resection. However, the additional benefit of portal vein resection is still controversial. To reduce the misunderstanding, we changed the term "radical resection" to "curative resection". The "curative resection" means achieving negative surgical margins regardless of the extent of resection.

**Why are you using a picture of a hepatocellular carcinoma.**

We changed the picture of HCC to the picture of hilar cholangiocarcinoma.

**Reviewer #4:**

In this mini Review the authors summarize the pros and cons of the currently available procedures carried out for pre-operative biliary drainage that help in the outcome of subsequent surgical removal of Klatskin tumor and associated partial hepatic resection. They finally conclude the method most appropriate for each or combination of different outcomes. The manuscript however needs the following changes to be provide appropriate information to the reader:

**1) The Title and Running Title need a small change – ‘of’ to ‘in’.**

We changed the Title and Running Title according to your suggestion.

Title: “Preoperative Biliary Drainage in Hilar Cholangiocarcinoma: When and How”

Running Title: “Preoperative Biliary Drainage in Hilar Cholangiocarcinoma”

**2) In the Abstract an important element is missing, namely the principal conclusions of the authors and the suggestions made. These should be included**

We added the conclusions and suggestions of this minireview in ABSTRACT session.

“Under certain special indications such as right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended. Generally, selective biliary drainage is enough before surgery, however, in the cases of development of cholangitis after unilateral drainage or slow resolving hyperbilirubinemia, total biliary drainage may be considered. Although the optimal preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended. ENBD seems to be the most appropriate method of PBD in terms of minimizing the risks of tract seeding and inflammatory reactions.”

**3) The Table will very likely be more presentable with an interchange of Rows and Columns. The ‘Study Design’ can easily be excluded since all reports are Retrospective which can be indicated with an \* at the end of the Table heading and its explanation at the bottom.**

We changed the TABLE 1 as you suggested.

	Total number of patients with PBD	PBD-associated morbidity	Serum bilirubin before surgery (mg/dL )	Duration of PBD (days)	Postoperative morbidity	Postoperative complications	Infectious complications	5-year survival rate
<b>Hochwald et al.<sup>[9]</sup>(1999)</b> *	42 (PTBD 23; ERBD 13; intraoperative 3; ENBD 1; PTBD and ERBD 1; ERBD and ENBD 1)	-	5.6 ± 0.9	-	90%	5%	52%	-
<b>Figueras et al.<sup>[10]</sup> (2000)</b> *	11 (PTBD 11)	-	11.0 ± 9.4	16 ± 10	100%	9%	18%	25%
<b>Ferrero et al.<sup>[11]</sup> (2009)</b> *	30 (PTBD 18; ERBD 7;	23%	3.1 (range 0.3-14.	27.5 (range 10-90)	70%	3%	11%	-



	ERBD and  PTBD 3;  intraoperati  ve 2)		1)					
<b>Kloek et al.<sup>[12]</sup> (2010) *</b>	101 (PTBD 11; ERBD 90)	76%	PTBD  1.1 ± 0.8;  ERBD  1.3 ± 1.2	PTBD  11  (3-21);  ERBD  15  (4-29)	-	-	48%	-
<b>Grandadam et al.<sup>[13]</sup> (2010) *</b>	12 (PTBD 12)	25%	4.1 ± 2.5	32 ± 9	13%	0	-	42%
<b>Kawakami et al.<sup>[14]</sup> (2011) *</b>	128 (PTBD 48; ERBD 20; ENBD 60)	Total 40%  (PTBD 31%;  ERBD 65%;  ENBD 38%)	10.5  (range 2.2-29.3)	11.4  (range 1-154)	13%	3%	-	-
<b>Ratti et al.<sup>[15]</sup> (2013) *</b>	55 (PTBD 51; ERBD 4)	18%	3.4 ± 1.5	24  (range 10-36)	46%	5%	7%	29%
<b>Farges et al.<sup>[8]</sup> (2013) *</b>	180 (PTBD 104; ERBD 63; PTBD	33%	2.8  (range 1.2-5.6)	32	68%	9%	-	-

	and ERBD							
	13)							

\*All reports were retrospective studies.

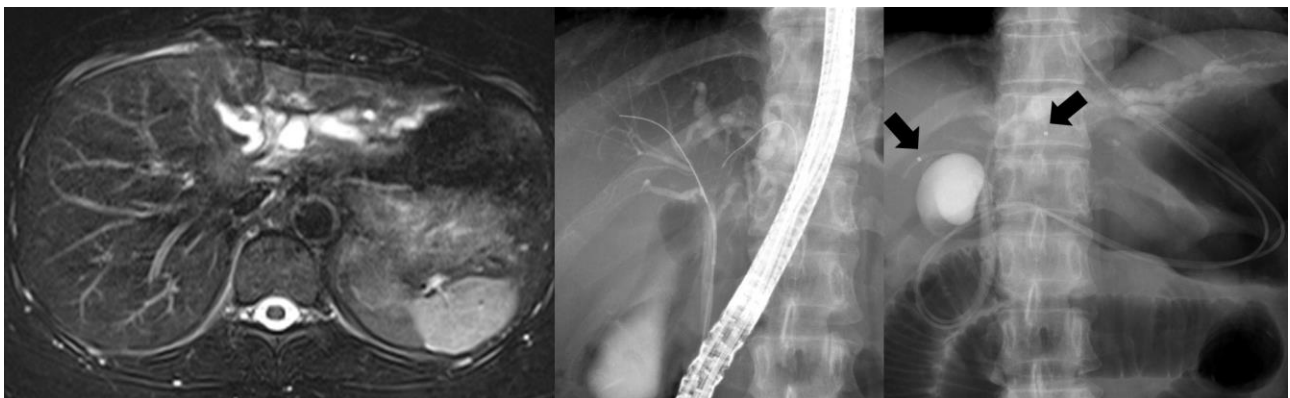
Data are expressed as mean  $\pm$  standard deviation or median (range).

PBD, preoperative biliary drainage; PTBD, percutaneous transhepatic biliary drainage; ERBD, endoscopic retrograde biliary drainage; ENBD, endoscopic nasobiliary drainage.

**4) The single Figure in the paper depicts a case not of Klatskin tumor but of HCC with hilar biliary obstruction. Therefore the advantage of ENBD in highlighting biliary tracts in both hepatic lobes should be pointed out in the illustration heading and also in the figure.**

We changed the Figure 1 to the case of Klatskin tumor according to the Reviewer #3's comments, and we gave an explanation about the figure as follows.

**"Figure 1.** 49-year-old female with Bismuth type IIIB hilar cholangiocarcinoma. Since contrast media were injected into both intrahepatic biliary ducts, bilateral endoscopic nasobiliary drainage was performed to prevent post-procedural cholangitis (Black arrows indicate the tip of nasobiliary tubes)."



**5) Some language and grammatical changes throughout the text need to be done.**

According to the reviewer's suggestion, the manuscript was revised again by a native speaker.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Endoscopy*.

Sincerely yours,

Jin-Hyeok Hwang

Professor, Department of Internal Medicine

Seoul National University College of Medicine, Seoul National University Bundang Hospital

166 Gumi-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 463-707, Korea

Tel: +82-31-787-7017/Fax: +82-31-787-4051

e-mail: woltoong@snu.ac.kr